

Jarl Risberg

Mental Functions

Studied with Multi-Regional Measurements of the
Cerebral Circulation

Lund 1973

MENTAL FUNCTIONS STUDIED WITH MULTI-REGIONAL
MEASUREMENTS OF THE CEREBRAL CIRCULATION

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JARL RISBERG
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From the Department of Clinical Neurophysiology,
University Hospital, and the Department of Psychology,
University of Lund, Lund, Sweden.

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STUDIES IN THE EFFECTS OF NOISE ON HUMAN
HEARING AND THE EFFECTS OF NOISE ON
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The present thesis is based upon the following papers:

- I. J. Risberg and D.H. Ingvar:
Patterns of activation in the grey matter of the dominant hemisphere during memorization and reasoning. A study of regional cerebral blood flow changes during psychological testing in a group of neurologically normal subjects.
Brain, submitted for publication, 1973.
- II. L. Gustafson and J. Risberg:
Regional cerebral blood flow related to psychiatric symptoms in dementia with onset in the presenile period.
Acta psychiatr. scand., submitted for publication, 1973.
- III. J. Risberg and D.H. Ingvar:
Multibolus technique for measuring the distribution of cerebral blood flow over short intervals in man.
Circ. Res., 31, 889-899, 1972.
- IV. J. Risberg and D.H. Ingvar:
Increase of regional cerebral blood volume during REM-sleep in man. In: Proc. of the First European Congress of Sleep Research, Basel, Oct. 3-6, 1972. Edited by W. Koella, Karger, Basel, 1973, in press.
- V. J. Risberg, D. Ancrì, and D.H. Ingvar:
Correlation between cerebral blood volume and cerebral blood flow in the cat.
Exp. Brain Res., 8, 321-326, 1969.

The papers will be referred to by the roman numbers.

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INTRODUCTION

The present thesis concerns the physiological basis of the mental functions. Our present knowledge of the mechanisms underlying memory, speech, problem solving, imagination, etc., is very limited indeed. Most of our knowledge is based on studies of psychological effects of brain lesions (BROCA 1861, WERNICKE 1874, LASHLEY 1929, GOLDSTEIN 1942, SCOVILLE and MILNER 1957, LURIA 1966, and many others) and of electrical stimulation of the cortex (PENFIELD and JASPER 1954).

Recordings of the scalp EEG made possible for the first time recordings of cerebral events coupled to mental functions in the intact man (BERGER 1929, MUNDY-CASTLE 1957, and others). In recent years, evoked potentials and the contingent negative variation have been used with success in the study of physiological correlates to attention and information processing (WALTER et al. 1964, SUTTON et al. 1965, SMITH et al. 1970, BARLOW 1971, and many others). The electrophysiological phenomena which accompany mentation (for example blocking of the alpha rhythm) are still, however, in many respects unexplained.

In the studies summarized here, the potentialities of a new cerebral parameter in the study of higher mental functions, the regional cerebral blood flow (rCBF), have been explored.

Cerebral circulation and mental functions.

The first observations of cerebral circulatory changes related to mental activity were made by MOSSO (1881). He studied patients with cranial defects and reported increases in brain volume and brain pulsations during mental arithmetics as well as in conjunction with emotional reactions.

Early observations of changes of cerebral circulation during mental activity were also described by FULTON (1928). He reported that the bruit over an arterio-venous aneurysm in the occipital pole augmented during visual activity (reading). The change in the bruit occurred 20-30 seconds after the start of the reading and continued during the task to decline when the patient had finished reading.

In 1945 the first method was developed which made measurements of total mean cerebral blood flow (CBF) and oxygen uptake (CMRO_2) in the intact man possible (KETTY and SCHMIDT 1948). Many clinical groups have been investigated with this method, which is based on nitrous oxide inhalation. Several studies have shown that patients with organic dementia have subnormal CBF and CMRO_2 (FREYHAN et al. 1951, LASSEN et al. 1957, and others). This method has, however, been used in only one study of mental activity in normals. In contrast to the findings summarized below, SOKOLOFF and coworkers (1955) did not find any significant difference in mean CBF and CMRO_2 between the resting state and the solving of arithmetic problems in 13 normal young volunteers. On the contrary, there was in fact a slight tendency to

a diminution of CBF during the test. To explain the findings it was proposed that both regional augmentations and diminutions could have taken place during mental activity and hence the net CBF effect was nil. This interpretation was supported by the later findings in cats made by the same author (SOKOLOFF 1961) that a local CBF increase in the striate area during visual stimulation was accompanied by a flow diminution in the surroundings. Findings of this type were later also made in two human subjects by COOPER and coworkers (1966) by means of a thermistor technique for relative blood flow measurements. Their study demonstrated clearly a very strict localization of the blood flow changes in the occipital pole during visual activities. Reading was accompanied by flow increases in the striate area as well as in the surrounding secondary visual regions, while intermittent photic stimulation only augmented the flow in the striate area proper.

The intra-arterial $^{133}\text{Xenon}$ injection technique for quantitative measurement of regional cerebral blood flow through the intact skull (rCBF; LASSEN and INGVAR 1961, LASSEN et al. 1963, HØEDT-RASMUSSEN et al. 1966, LASSEN and INGVAR 1972) offered new possibilities in the study of physiological correlates to mental functions. In the investigations summarized here and in their forerunners (INGVAR and RISBERG 1965; 1967, RISBERG 1968, RISBERG and INGVAR 1968 a and b; 1970; 1971/72) it is demonstrated that the performance of mental tasks is accompanied by localized increases of the cerebral blood flow, which with all likelihood are caused by increases in the local neuronal activity.

In contrast to the findings of SOKOLOFF et al. (1955) significant increases of the hemisphere mean CBF are demonstrated in the present studies. The average changes were, however, relatively small (10-15 per cent) and showed considerable individual variations (0-30 per cent). Such changes might be difficult to demonstrate with the nitrous oxide technique which has a considerably larger random measurement error than the $^{133}\text{Xenon}$ clearance technique (KETTY and SCHMIDT 1948, I). As has been pointed out elsewhere (INGVAR and RISBERG 1967) the negative results of SOKOLOFF et al. (1955) might also be related to the fact that in their study the mean CBF level at rest was about 30 per cent above the reported normal values in resting young healthy subjects (KETTY and SCHMIDT 1948), possibly due to anxiety or apprehension.

The principle aims of the present studies were:

- A/ to develop and validate radioisotope methods especially suited for psycho-physiological investigations (III and V)
- B/ to establish the normal patterns of rCBF changes during different types of mental activity (I and III)
- C/ to study regional cerebral circulatory changes during REM- (Rapid Eye Movement-) sleep (IV)
- D/ to study the relationship between the degree of mental deterioration and the diminution of CBF (at rest) in different cerebral regions in patients with organic dementia (II)

A. TECHNIQUES USED IN THE PRESENT STUDIES FOR MEASUREMENT OF REGIONAL CEREBRAL CIRCULATION.

1. The intra-arterial $^{133}\text{Xenon}$ injection technique.

This technique for measurement of regional cerebral blood flow (rCBF) is described in detail in paper I (INGVAR and LASSEN 1961, LASSEN et al. 1963, HØEDT-RASMUSSEN et al. 1966, INGVAR and GUSTAFSON 1970, OLESEN et al. 1970, SVEINSDOTTIR et al. 1971/72, LASSEN and INGVAR 1972, RISBERG et al. 1973). In short, it implies a rapid (1-2 sec.) injection into one of the internal carotid arteries of an inert diffusible gamma-emitting indicator, $^{133}\text{Xenon}$. The clearance of the isotope, which takes 15 minutes, is recorded externally by multiple (8 or 32) scintillation detectors. A clearance curve is obtained from each region of measurement and on the basis of this curve different parameters are calculated, which estimate the flow through the grey (fast) and white (slow) matter separately, and also gives an estimate of the relative weight of these two tissues.

Advantages: rCBF is determined quantitatively with high accuracy (correlations between repeated resting measurements between 0.91 and 0.98 for the hemisphere mean values corresponding to a random measurement error of 3.5-5 % ; INGVAR et al. 1965, MCHENRY et al. 1969; I) and spatial resolution (several hundreds of detectors might be used to cover the hemisphere; SVEINSDOTTIR et al. 1973).

Disadvantages: The main disadvantage of the $^{133}\text{Xenon}$

method is the need for a carotid puncture. Clinical measurements have usually been made in patients submitted for carotid angiography. However, the complication rate in about 4.000 rCBF studies has been found to be very low with permanent sequelae in only 0.2 % of the studies (INGVAR and LASSEN 1973). Practically all of these occurred in patients with severe intracranial disorders.

The carotid puncture also involves some stress, which might influence the rCBF determinations. The minimal time interval between two studies is about 17 min., which does not allow detailed studies of rapid flow changes.

2. The multibolus technique.

The multibolus technique, presented in paper III, was developed recently for short interval measurements (one min. between determinations) of the regional distribution of CBF. Following an initial conventional rCBF determination, according to the method described above, equal amounts of a $^{133}\text{Xenon}$ solution are injected into the internal carotid artery at one minute intervals. Extracranial recordings of the gamma-radiation are made in multiple hemisphere regions by means of multiple scintillation detectors. Following each injection in this multibolus series, a sudden increase in activity is recorded from each brain region. The complete series yielded a slowly rising saw-tooth curve for each region. The perpendicular heights of these curves are a measure of the amounts of isotope arriving at each region of the brain following each injection and this amount of isotope is proportional to the flow of the region,

according to the bolus fractionation principle (SAPIR-STEIN 1964). If the mean hemisphere blood flow is unchanged during the multibolus series, the method gives absolute flow values for each region. However, if the total flow varies during the series, the regional flows relative to the mean hemispheric blood flow are obtained rather than the absolute values of regional flow.

The principle of the method might be used in other organs than the brain.

Advantages: The method has a high temporal and spatial resolution and, according to the results in paper III, a small error of measurement (about 4 per cent).

Disadvantages: A carotid puncture is needed also with this technique (see above). The method is quantitative only if the hemispheric average flow is unchanged during the measurements.

3. The rCBV-method.

The regional cerebral blood volume (rCBV-) method implies an intravenous injection of an intravascular non-diffusible gamma-emitting indicator, for example ^{131}I -labelled human serum albumin (RISA; RISBERG 1968, RISBERG and INGVAR 1968 a and b; 1970). After the tracer has mixed completely with the blood, a relative measure of cerebral blood volume is obtained by recording of the radiation over the head by means of multiple scintillation detectors. The changes observed are relatively small, in the range of 1 to 5 per cent (see below).

Validation of the rCBV-method.

In paper V, blood flow and blood volume were measured simultaneously in the same cerebral region in anesthetized cats with controlled respiration. The measurements were made with the same scintillation detector using ^{133}Xe for flow determinations and the intravascular indicator RISA (^{131}I) for volume recordings. A very high correlation was found between volume and flow changes ($r = .96$, $p < 0.001$). This finding indicates that variations of regional cerebral blood volume are accompanied by proportional blood flow changes. The blood volume changes were, however, found to be of much smaller magnitude than the flow changes, a doubling of CBF was accompanied only by a 14 % increase of CBV. A linear relationship between CBV and CBF was also found by SMITH et al. (1971) in goats. They found, however, that a doubling of CBF was accompanied by a 27 % increase in CBV, thus a larger value than was found in the present study in cats. GRUBB and coworkers (1973) using a recent X-ray fluorescence technique for absolute rCBV measures (TER-POGOSSIAN et al. 1971/72) found the corresponding CBV increase in monkeys to be 28 %. These results indicate that the CBV-CBF relationship might be somewhat different between species (small - large brains). It can, however, be concluded that the present rCBV-method, as used in man, gives an index of changes of rCBF. The magnitude of the rCBV changes must be small, since a 20 % rCBF increase approximately corresponds only to a 3-5 % rCBV increase.

The blood pool of the scalp and skull amounting to about 30 % of the total blood content of the head (OLDENDORF

1969, V), is also recorded in the rCBV measurements. There is, however, good reason to assume that the extra-cerebral blood volume is fairly constant during REM-sleep (IV) and during mental effort (RISBERG 1968, RISBERG and INGVAR 1968 a and b).

An increase in the arterial blood pressure, which might accompany psychic activity (I) and also REM-sleep (SNYDER et al. 1963), would give rise to a global decrease in cerebral blood volume, due to the autoregulatory mechanisms of the brain. The results obtained from measurements during mental activity (RISBERG 1968, RISBERG and INGVAR 1968 a and b; 1970), now confirmed in papers I and III, showed, however, specific regional patterns of rCBV increases and decreases. Such changes, which also are seen during REM-sleep (IV), can not be explained by any systemic circulatory changes.

Advantages: The main advantage is the completely atraumatic nature of the method which makes measurement in normal volunteers during longer periods (nights) possible. The time resolution of the method is relatively high (1 min. between determinations). The method offers special advantages for sleep studies.

Disadvantages: The rCBV method is relative, offering an index of cerebral circulatory changes. As was discussed above the measurements might be influenced by changes in the extra cerebral blood content and by systemic circulatory changes. The methods does not allow measurements in more than about 8 regions of each hemisphere, due to the relatively low counting rates obtained. Only larger cerebral circulatory changes can

be detected in the single measurements because of the small magnitude of the rCBV changes (normally 3-5 per cent, cf. RISBERG et al. 1969 b).

B. REGIONAL CHANGES OF CORTICAL BLOOD FLOW DURING REASONING AND VISUAL AND AUDITORY MEMORIZATION (I and II).

Multi-regional measurements of cerebral blood flow were made in 21 neurologically normal subjects during the performance of different psychological tests. Statistically significant increases of the mean hemispheric flow, averaging about 10 per cent, were seen during the tests. Different patterns of increases and decreases of the grey matter blood flow were also seen which in some respects were specific to the type of mentation going on. As is indicated in Fig. 1, a reasoning test involving visual activities gave an augmentation of grey matter blood flow of up to 25 per cent in occipital, temporo-occipital, parietal, prerolandic, and frontal structures, while an auditory digit-span-backward test was accompanied by augmentations in frontal, prerolandic, and posterior temporal regions mainly. A visual memory test was accompanied by a rCBF redistribution with increased flow in occipital, parietal, and temporo-occipital structures, and decreases over rolandic regions (III).

There is considerable evidence supporting the assumption that the regional flow changes demonstrated indicate changes of local neuronal activity (KETY 1950, LASSEN 1959, WAHL et al. 1971, cf. I).

The activation patterns found are in accordance with well established concepts about the participation of the cortex in sensory-motor and language functions, supposed to be involved in the performance of the pre-

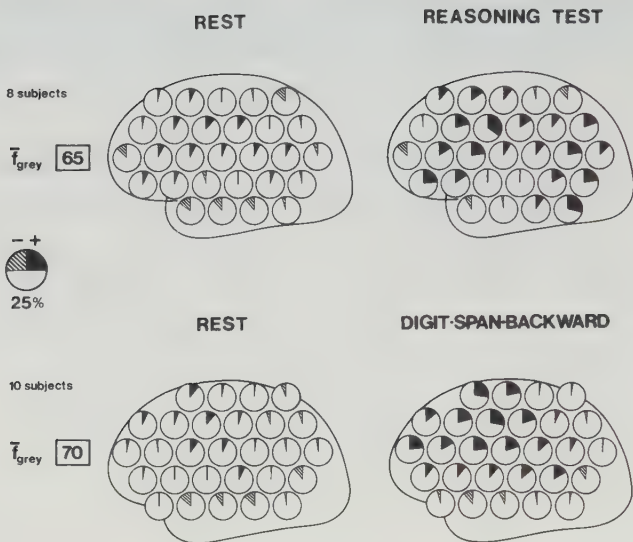


Figure 1. Average changes of grey matter blood flow (f_{grey}) in ml/100 g/min. in neurologically normal subjects during the reasoning test and during the digit-span-backward test (adapted from paper I). The clock symbols should be read thus: 12 o'clock denotes the mean value at rest for the whole group (8 and 10 subjects respectively) for all regions measured (e.g. 65 ml/100 g/min. for upper row indicated in the box). Black marking in the circles denotes a value above the reference value, and striped fields denotes values below the mean (90° = 25%). It is clearly seen that the two tests gave different flow patterns (see text).

sent psychological tests. The anterior frontal "association" cortex, which showed large flow increases, during the digit-span-backward test and the reasoning test, has been supposed to be involved in problem solving, logical operations, etc. (PENFIELD and JASPER 1954, LURIA 1966).

Considerable individual variations were seen in the mean hemispheric changes during the tests (0-30 %). The inter-regional differences in cortical flow during mental activity, without regard to the average changes, were on the contrary fairly similar within the group.

On the basis of these findings it is proposed, in accordance with well established neurophysiological concepts, that the cortical flow increases during mental activity consists of two components:

1/ A non-specific component determined by the general level of arousal, during the tests and, probably mediated by the reticular activating system (MAGOUN 1963). This component could also, it seems, be intimately related to motivational and emotional functions (LINDSLEY 1951).

2/ A specific component giving rise to a more circumscribed cortical activation related to selective attention (BROADBENT and GREGORY 1963, BROADBENT 1970). The regions activated depend upon the type of mentation going on.

C. REGIONAL CEREBRAL CIRCULATION DURING REM-SLEEP (IV).

It is thus well established that mental activity in man awake is accompanied by increases of the local cortical blood flow. Much less is known about cerebral circulation during the mental activity of sleep, dreaming, which has been found to be linked to the REM- or para-sleep stage (ASERINSKY and KLEITMAN 1953, DEMENT and KLEITMAN 1957). It has been shown by KANZOW et al. (1962) and by REIVICH et al. (1968) in cats and by SEYLAZ et al. (1971) in man, that REM-sleep is accompanied by a markedly increased cerebral blood flow level.

As was indicated above, the rCBV method has certain advantages for sleep studies and was used in normal volunteers for measurements during physiological sleep (RISBERG et al. 1969 a; IV). In paper IV, the results from measurements in 7 subjects showed that the largest and most significant circulatory increases during REM-sleep took place in prefrontal and parietal regions. It was also demonstrated that the cerebral circulation changes markedly within the REM-sleep period in accordance with the appearance of REM:s. Periods with high frequency of REM:s were coupled to a relatively higher cerebral blood volume, while silent (tonic) periods with no REM:s were coupled to a relatively lower circulatory level. The difference in rCBV was in the range of 3-5 % corresponding to blood flow increases of about 20 % (V). These changes could not be explained by respiratory or systemic circulatory changes.

The results are in accordance with the general view that during REM-sleep the cerebral cortex is as active as

during wakefulness (KLEITMAN 1963, cf. BERGER 1969). The correlation found between rCBV and the REM-frequency fits with the findings of a relationship between the amount of REM:s and the intensity and vividness of the dream (BERGER and OSWALD 1962).

In view of the relatively large rCBV increase found in the parietal region, it is inviting to suggest that this region is involved in dreaming, especially since this region is known to be important for other integrated activities of the visual system in wakefulness, like spatial thinking etc. (CRITCHLEY 1953, LURIA 1966).

It can be concluded that REM-sleep (dreaming) is accompanied by increases and redistributions of the cerebral circulation which are similar to changes found during mental activity in the wake man. For the first time, circumscribed parts of the hemisphere (the parietal and fronto-orbital regions) have been demonstrated to be involved in dreaming.

D. rCBF RELATED TO PSYCHIATRIC SYMPTOMS IN PATIENTS WITH ORGANIC DEMENTIA (II).

The diagnostic problems in patients with mental deterioration (organic dementia) are well known and there is a great need for quantitative diagnostic methods based upon cerebral indices. In the study summarized here, and in its forerunners, in which parts of the present material have been presented (OBRIST et al. 1970, INGVAR and GUSTAFSON 1970), the diagnostic potentialities of the rCBF method in psychiatric practice have been further explored.

rCBF was measured in 8 regions of the dominant hemisphere in 50 patients with presenile dementia. Patients with symptoms mimicking dementia secondary to psychosis were excluded, as well as patients with severe alcoholism or drug addiction. The patients showed the classical symptoms of mental deterioration, amnesia, agnosia, apraxia, and disturbances of attention and concentration, etc. (GUSTAFSON 1973). These symptoms were rated by a psychiatrist (Lars Gustafson) and so were the symptoms of anxiety, mood changes, paranoid and other delusions, changes of psychomotor activity, etc. The ratings of 67 symptoms were factor analyzed and the 14 factors obtained (GUSTAFSON 1973) were correlated to the rCBF variables. Three factors containing symptoms of pronounced mental deterioration like amnesia, apraxia, agraphia, aphasia, showed the largest negative correlations to rCBF and relative per cent of grey matter in posterior temporal and temporo-parietal regions, suggesting that the most demented patients have a reduced oxygen uptake and cortical atrophy in these reg-

ions. The earlier productive symptoms of affective or other changes of personality in organic dementia were mainly found in patients with a relatively better preserved cerebral circulation. Patients with paranoid symptoms had a high grey matter flow, especially frontally in combination with decreased flow in the posterior temporal region. Changes of psychomotor activity correlated to the relative weight of grey matter in the motor region.

On the basis of the correlations shown between psychiatric symptoms and various flow patterns, it is concluded that the rCBF technique can be applied to measure quantitatively general or regional cerebral dysfunction underlying various forms of dementia.

GENERAL COMMENTS

The studies summarized above demonstrate that multi-regional measurements of cerebral circulation can in a new way provide quantitative measures of physiological changes in the grey matter of the brain related to mental functions. It is now well established that the blood flow of different cortical regions is regulated according to the local functional activity. rCBF-values measured in awake subjects are thus always more or less influenced by sensory stimulation and possible motor activity (movements, speech; OLESEN 1971) involved in the measurement procedure. It is obvious that the measurement situation has to be "standardized" as far as possible in all measurements of rCBF in order to obtain reliable and reproducible results.

Rather extensive but still circumscribed parts of the cerebral hemisphere were found to augment their blood flow during the complex mental functions involved in the performance of the different tests. The results have clearly demonstrated that higher mental functions are not strictly localized to small cortical zones, as proposed by the localizationists (MEYNERT 1867, KLEIST 1934, and others), nor do they suggest that the brain does not have any functional differentiation at all with respect to mental functions, as proposed by the anti-localizationists and the noetic school (FLOURANCE 1824, LASHLEY 1929, GOLDSTEIN 1942, and others).

There are modern theories which unify the earlier hypotheses, f ex. the dynamic localization theory proposed by LURIA (1966) which derives several concepts from the

earlier writings of HUGLINGS JACKSON and PAVLOV. LURIA's theory - which appears to fit the present results excellently - proposes a graded localization of functions, with a more narrow and specific localization in the primary and secondary projective fields ("nuclear zones of analysers", cf. the selective activation of the auditory and visual fields during the different tests used), and a more unspecific "pluripotential" function of the overlapping tertiary, or association cortex. His theory thus agrees well with the present findings of a large increase in the anterior frontal association cortex both during the digit-span-backward test and the reasoning test. The posterior association cortex was also activated by both tests although not as pronounced.

In spite of the positive results obtained with the present methods, it must be stressed that the techniques used are gross. The mean blood flow of all cortical layers within the region recorded, is calculated, with predominance of the superficial lateral hemisphere structures. New methods will, however, permit measurements in circumscribed regions of the depth of the brain of the local oxygen uptake, CBF, or CBV. (TER-POGOSSIAN et al. 1969, 1971/72).

The psychological tests used here naturally only represent a minimal part of all possible types of mental activity, and information has only been obtained from the dominant hemisphere. Further measurements are needed especially concerning changes in the non-dominant hemisphere during verbal versus non-verbal activities.

There is also a need to investigate further the present finding that the rCBF-patterns "focalize" during repeated administration of the tests. This suggests that the rCBF method, in addition to electrophysiological techniques, might be used with advantage to study learning, habituation and conditioning mechanisms directly in the brain. Furthermore, the individual variations in the general and local flow changes observed should be related to emotional and motivational factors and, finally, the coupling between the rCBF patterns and various cognitive strategies pertaining to personality variables (RISBERG 1968) should be further elucidated.

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